REMARKS

Claims 35-65 are pending in this application and claims 43-50 and 59 are under consideration. Claims 35-42 were withdrawn from consideration by the Examiner in view of the Restriction Requirement dated May 23, 2005. Claims 51-58 and 60-65 are currently withdrawn from consideration by the Examiner following the Election of Species Requirement dated May 23, 2005, but will be rejoined following the allowance of a generic claim.

The issues raised in the outstanding Office Action dated September 9, 2005 will be addressed below in the order raised in the Office Action.

I. Election/Restriction.

Claims 43-50 and 59 were examined in the pending application. Applicants note that claims 51-58 and 60-65 are drawn to non-elected species and will be subject to examination upon the finding of an allowable generic claim.

II. Claims 43-50 and 59 are Patentable over Standeven et al. in view of Koyama et al.

Claims 43-50 and 59 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Standeven et al. (Fundamental and Applied Toxicology 34:91(1996)) (*hereinafter,* "Standeven") in view of Koyama et al. (Developmental Biology 208:375 (1999) (*hereinafter,* "Koyama"). In particular, the Office Action states that in Standeven it is "stated that Retinoids inhibit chondrogenesis, and that this effect on the epiphyseal plate closure was blocked by the RAR antagonist." *See,* Office Action, page 2-3. The Office Action further states that Koyama "teaches that the antagonists are necessary for chondrocyte development and for endochondral ossification." *See,* Office Action, page 3. The Office Action concludes that the instant method would have been obvious given the teachings of Standeven and Koyama. *See,* Office Action, page 3. Applicants respectfully disagree.

As an initial point, the model described in Standeven is not designed to evaluate new cartilage formation at all -- the purpose of this work was to evaluate epiphyseal plate closure and retinoid-induced bone toxicity as well as to identify a

suitable in vivo model for retinoid-induced epiphyseal closure. Standeven's model system is not relevant at all to chondrogenesis as presently claimed. Thus, the work of Standeven would not have provided any disclosure or suggestion of a method of stimulating chondrogenesis whatsoever, as the ordinarily skilled worker would have recognized that **Standeven's model system was designed to evaluate epiphyseal plate closure and not chondrogenesis**.

Applicants further submit that Standeven discusses the combined use of a retinoic acid receptor (RAR) agonist and antagonist. In Standeven, the epiphyseal plate closure caused by the agonist was blocked by co-treatment with a five-fold molar excess of the antagonist. *See,* Table 4. The antagonist was used in Standeven to counteract the effects of the agonist (retinoid) on the epiphyseal plate closure (*see*, Standeven, Table 4), as is stated in the Office Action, pages 2-3. Thus, the antagonist is used to block epiphyseal plate closure and not to stimulate chondrogenesis. In fact, nowhere in the Standeven reference is a RAR antagonist used alone to stimulate chondrogenesis. RAR antagonist was administered alone to a control group, but there was no discussion of the RAR antagonist stimulating chondrogenesis. The focus of Standeven is exclusively on epiphyseal plate histology, and RAR antagonist treatment was described as resulting in "normal Epiphyseal plate histology." *See*, Standeven, page 94, second column, last paragraph, to page 95, first column, lines 1-6 and Table 4. The study does not evaluate the effects of RAR antagonist on chondrogenesis and, indeed, Standeven could not have looked at new cartilage formation in his model system.

Further, in Koyama an implanted bead of antagonist was used and in ten days it was found that the humorous was small in size, contained only immature chondrocytes and had not undergone endochondral ossification. Further, chicken embryos were treated with RAR antagonists where such treatment was described as resulting in "severely affected humorous development" and the prevention of endochondral ossification (*see*, Abstract). This reference does not teach the use of a RAR antagonist alone to stimulate chondrogenesis, as is disclosed in the present application.

Accordingly, the applicants respectfully submit that both of the cited references demonstrate a requirement for retinoid signaling in chondrocyte maturation. Specifically, they show the requirement for RAR agonists in chondrocyte maturation and hypertrophy. Further, they demonstrate that, in contrast, RAR antagonists inhibit chondrocyte maturation and hypertrophy. They do not discuss any role of a RAR antagonist in chondrogenesis.

Chondrogenesis is a multi-step process that involves the commitment of mesenchymal cells to the chondrogenic lineage, formation of pre-cartilaginous condensations by committed chondroprogenitors, differentiation of chondroprogenitors into chondroblasts or chondrocytes and maturation of chondrocytes into hypertrophic chondrocytes. The cited references look at the effect of retinoid action **late in chondrogenesis during the maturation of chondrocytes into hypertrophic chondrocytes**. In contrast, in the presently claimed invention RAR antagonists are used to **promote chondrogenesis**, the stage involving the differentiation of chondroblasts or chondrocytes. More specifically, the cited references examine the action of retinoid manipulation using agonists and antagonists on an **existing mature chondrogenic template** (in both instances, the growth plate), whereas the presently claimed invention is directed to the **generation of the chondrogenic template** using RAR antagonists.

In addition, the present invention is directed to the use of RAR antagonists to stimulate new cartilage formation and not to remodel existing cartilage, which is a different phenomenon. Further, there is a distinct difference between **newly formed cartilage**, which is the focus of the present invention, and the type of mature cartilage being addressed by the cited references. Thus, in the present invention, methods to stimulate cartilage formation are claimed and not methods to stimulate formation of hypertrophic or mineralized cartilage from mature cartilage as discussed in the cited references. Furthermore, the claimed methods do not use any agonist, and the antagonists of the present invention are not used to reverse any type of cartilage hypertrophy as described in Standeven. Standeven and Koyama are looking at the effects of RAR antagonists on RAR signaling. In other words, they are

trying to reverse the effects of RAR agonists. They do not assess the effects of RAR antagonists alone on new cartilage formation.

In summary, the cited references are looking at the effects of RAR agonists on the growth plate, and use RAR antagonists to block RAR signaling. Neither of the cited references, taken alone or together, disclose or suggest a method of stimulating chondrogenesis using an RAR antagonist as presently claimed.

Finally, Applicants would like to emphasize that until the presently claimed invention, stimulation of cartilage formation by RAR antagonists had not been demonstrated. Based on the prior art it would not have been obvious that antagonism of retinoid signaling would stimulate chondrogenesis, especially through promotion of chondrobast differentiation. Accordingly, Applicants respectfully submit that the combined teachings of the cited references fail to teach or suggest a method for stimulating chondrogenesis or new cartilage formation at all, including such a method using RAR antagonists as is described in the present invention.

III. Conclusion.

The concerns of the Examiner having been addressed in full, the Applicant respectfully requests withdrawal of all outstanding rejections and the issuance of a Notice of Allowance forthwith. The Examiner is encouraged to address any questions regarding the foregoing to the undersigned attorney, who may be reached at (919) 854-1400.

Respectfully submitted,

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